REMARKS

Applicants acknowledge that the Examiner has considered the application eligible for continued examination under 37 C.F.R. § 1.114, that the fee set forth under 37 C.F.R. § 1.17(e) has been timely paid, and that the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicants also note that the amendment filed November 12, 2002 has been entered. Accordingly, claims 1, 55, 60, 75 and 87-94 are currently pending in the instant application.

Claims 1, 55, 60 and 75 have been currently amended. Support for the amendments can be found throughout the application as filed and specifically in Example 3 on pages 34-35 and Example 4 on pages 35-36. The specification has also been amended to correct minor clerical errors. It is submitted that no new matter has been added as a result of these amendments to the claims and specification.

I. Correction of Attorney Docket Number

Applicants filed a request for Power of Attorney, Revocation of Prior Powers and Change of Correspondence on April 9, 2002 in which Applicants requested that the Attorney Docket Number for this application be changed from the former GIN-005 to the instant 36119-126US1. This request was acknowledged by the USPTO in a Notice on April 17, 2002. Unfortunately, the outstanding Office Action continues to use the former Attorney Docket Number GIN-005. Applicants respectfully request that the Attorney Docket Number be corrected to 36119.126US1 in future correspondence.

II. Petition to Correct Inventorship

As stated in the June Declaration under 37 C.F.R. § 1.132, filed November 12, 2002, Bruce L. Levine is also a co-inventor of the claimed subject matter. Applicants

submit herewith in the attached Appendix A, a Petition to Correct Inventorship under 37 C.F.R. § 1.48(a) to add Bruce L. Levine as a co-inventor in the instant application. The Petition includes the requisite (i) request to correct inventorship that sets forth the desired inventorship change under 37 C.F.R. § 1.48(a)(1); (ii) statement from Bruce L. Levine that the error in inventorship occurred without deceptive intention on his part under 37 C.F.R. § 1.48(a)(2); (iii) declaration by Bruce L. Levine under 37 C.F.R. § 1.63 as required by 37 C.F.R. § 1.48(a)(3); (iv) processing fee set forth in 37 C.F.R. § 1.48(a)(4); (v) written consent of the three assignees of this invention under 37 C.F.R. § 1.48(a)(5); (vi) statement under 37 C.F.R. § 3.73(b) from each of the three assignees; and (vii) copies of the executed Assignments of each co-inventor. Applicants respectfully request that the Petition be considered and that inventorship be corrected to reflect all co-inventors, including Bruce L. Levine, of the instant application.

III. Rejection under 35 U.S.C. § 102(f)

Claims 1, 55, 87-90, 92 and 94 stand rejected under 35 U.S.C. § 102(f) because the Examiner alleges that the Applicants did not invent the subject matter.

Upon entry of the Petition to Correct Inventorship, which correctly names five co-inventors, including Bruce L. Levine, the ground for this rejection has been overcome. Applicants therefore respectfully request withdrawal of this rejection.

IV. Rejection under 35 U.S.C. § 102(a)

Claims 1, 55, 87-90, 92 and 94 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Levine et al. With the entry of the instant Petition to Correct Inventorship, and in light of the June Declaration under 37 C.F.R. § 1.132, filed November 12, 2002, the Levine reference is not by "another" and, therefore, does not

qualify as prior art under 35 U.S.C. § 102(a). Thus, the ground for this rejection has been overcome. Accordingly, Applicants respectfully request withdrawal of this rejection and reconsideration of the Application.

V. Rejection under 35 U.S.C. § 102(e) based on Chang

Claims 1, 55, 60, 75, 87-89, 92 and 94 stand rejected under 35 U.S.C. § 102(e) as purportedly being anticipated by Chang, as evidenced by Levine et al.

Specifically, the Examiner alleges that "while Chang teaches and claims an *in vivo* method, Chang does teach the *in vitro* use of a microbead coupled with a plurality of binding molecules specific for an antigen on a human T cell, wherein the binding molecules are an antibody to CD3 and an antibody to CD28" (Office Action, page 4, section 8, paragraph 5). The Examiner also opines that the prior amendments to claims 60 and 75 do not result in a manipulative difference in the steps of the claims because the downregulation of HIV-1 fusion cofactors and an increase in resistance to infection by an M-tropic HIV isolate compared to a T cell not contacted would be inherent outcomes of the claimed methods (Office Action, page 4, section 8, paragraphs 6-8). The Examiner relies on Levine et al. for allegedly providing evidence "that resistance of T cells to infection with the M-tropic HIV-1 strain inherently occurs following contact with a solid phase surface comprising an anti-CD3 antibody and an anti-CD28 antibody *in vitro*" (Office Action, page 4, section 8, paragraph 9). The Examiner alleges that "downregulation of CCR5 also is inherent as evidenced by the resistance [of T cells] to infection by M-tropic HIV strains" (Office Action, page 4, section 8, paragraph 9). Finally, the Examiner purports that "the use of *in vivo* methodology equivalent to that disclosed in the specification-as-filed for *in vitro* experiments indicates that downregulation of CCR5 would be an inherent outcome of these methods, irrespective

of whether the contacting step is *in vivo* or *in vitro"* (Office Action, page 4, section 8, paragraph 7). Applicants respectfully traverse this rejection and request reconsideration based on the remarks that follow.

To anticipate a claim, a prior art reference must disclose ***each and every limitation*** of the claimed invention, either explicitly or inherently. See *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). Absence of a claim element from a prior art reference negates anticipation. *Atlas Powder Co. v E. I. du Pont de Nemours & Co., 750 F.2d 1569, 224 USPQ 409 (Fed. Cir. 1984)*. Anticipation of a patent claim requires a finding that the claim at issue "reads on" a prior art reference. See *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 781, 227 USPQ (BNA) 773, 778 (Fed. Cir. 1985). In other words, if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated, regardless of whether it also covers subject matter not in the prior art. *See id.* at 781.

Amended independent claims 1 and 55, and claims depending thereon, recite a method for downregulating HIV-1 fusion cofactor (or CCR5) expression in a T cell by contacting the T cell with a solid phase surface comprising an anti-CD28 antibody and an anti-CD3 antibody *in vitro*, to downregulate HIV-1 fusion cofactor expression in the T cell, wherein the T cell is more resistant to infection by an M-tropic HIV isolate than a T cell not contacted with the solid phase surface. Amended independent claims 60 and 75, and claims depending thereon, recite a method for downregulating HIV-1 fusion cofactor (or CCR5) expression in a T cell by contacting the T cell with a solid phase surface comprising an anti-CD28 and anti-CD3 antibody *in vivo* thereby downregulating HIV-1 fusion cofactor expression in the T cell, wherein the T cell is more resistant to infection by an M-tropic HIV isolate than a T cell not contacted with

the solid phase surface. Applicants respectfully submit that Chang fails to teach Applicants' claimed method.

In particular, Chang discloses immunoregulatory conjugates for use in ***activating T cells in vivo***, including a polymeric backbone coupled with binding molecules, for example, antibodies or antibody-derived fragments which bind to monovalent antigenic epitopes on CD3, epitopes of the T cell receptor, or other antigens on the surface of T cells, e.g., CD2, CD4, CD5, CD8, or CD28 (column 4, lines 39-52) or antibodies specific for HLA class-I antigens, HLA class II antigens, or anti-CD37 (col. 11, lines 32-36). Chang's teachings are directed to using immunoregulatory conjugates for ***inducing the polyclonal activation, proliferation, and/or lymphokine production of T lymphocytes*** (col.1, lines 15-18). Chang neither teaches nor appreciates the use of the disclosed immunoregulatory conjugates to ***downregulate HIV-1 fusion cofactor expression in a T cell, wherein the T cell is more resistant to infection by an M-tropic HIV isolate than a T cell not contacted with the solid surface.*** In addition, there is no teaching or suggestion in Chang to select antibodies that bind CD3 and CD28, among the laundry list of antibodies, which are taught to be equally useful for activating T cells *in vivo* to induce T cell activation, let alone to downregulate HIV-1 fusion cofactor expression. Chang, at best, merely provides an invitation to experiment. Applicants note that the Examiner, in agreement with Applicants' position, has acknowledged that "Chang did not appreciate that the results of administration of this product [a solid phase surface comprising an anti-CD28 antibody and an anti-CD3 antibody] would include downregulation of CCR5 expression in the T cell and an increase in resistance to infection by M-tropic HIV isolates compared to a T cell not contacted" (Office Action, page 4, section 8, paragraph 8).

However, the Examiner has alleged that Applicants have acknowledged that Chang describes *in vitro* methods. (Office Action, page 4, section 8, paragraph 4). Applicants respectfully disagree with this characterization of Applicants' submission. Applicants stated that "the only time Chang describes activation of T cells *in vitro* is to provide a rationale for his *in vivo* methods (see e.g., Chang, col. 11, lines 26-29)" (Paper No. 32). This is far from an acknowledgement that Chang ***teaches in vitro*** methods for downregulating expression of HIV-1 fusion cofactors, wherein the T cell is more resistant to infection by an M-tropic HIV isolate than a T cell not contacted with the solid phase surface. The Examiner has purported that the Chang teaches *in vitro* methods based on the disclosure at column 5, lines 31-37. Here, Chang reports that conjugates of the described invention can be used diagnostically to determine the number or proportion of T cells in a fluid sample using lymphocyte proliferation assays. But this is not a teaching of *in vitro* methods and more importantly, does not constitute an enabling disclosure for the *in vitro* use of a solid phase surface comprising an anti-CD28 antibody and an anti-CD3 antibody, for HIV-1 fusion cofactor downregulation, wherein the T cell is more resistant to infection by an M-tropic HIV isolate than a T cell not contacted with the solid surface. In contrast to the Examiner's position, Applicants respectfully assert that Chang does not teach <u>both</u> *in vitro* and *in vivo* methods to downregulate HIV-1 fusion cofactor expression. Instead, Chang ***teaches away*** from an ***in vitro*** method of ***activating T cells*** by teaching that a major concern with ***in vitro*** regimens

> is that the treatment is very tedious, expensive, and requires a sophisticated, specialized cell culture facility. The variation among cells or cultures from different patients requires demanding monitoring procedures. Also, ***lymphocyte cultures have very poor viability even under optimal conditions, meaning that during the culturing, large numbers of the cells will die.*** When large numbers of dead cells are injected into patients, this may actually burden the reticuloendothelial

> system (RES) and reduce its effectiveness in combating the tumor cells. [*emphasis added*]. See column 3, lines 19-27.

Because Chang expresses so many concerns with *in vitro* methods, it should be clearly apparent that Chang does not teach or suggest *in vitro* methods. Accordingly, Applicants respectfully assert that Chang provides no teaching or suggestion regarding a method for downregulating HIV-1 fusion cofactor expression by contacting T cells with a solid phase surface comprising anti-CD3 and anti-CD28 antibodies *in vitro*, wherein the T cell is more resistant to infection by an M-tropic HIV isolate than a T cell not contacted with the solid phase surface.

The Examiner has further opined that the downregulation of HIV-1 fusion co-factors and the resistance of T cells to infection with M-tropic HIV-1 strains would be inherent outcomes of the claimed methods. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d (BNA) 1746, 1749 (Fed. Cir. 1991). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* at 1269, 20 U.S.P.Q.2D (BNA) at 1749 (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

In the above-referenced application, Applicants have clearly described that (1) CCR5 transcripts were not detected in unstimulated T cells (page 38, line 22); and that (2) the HIV-1 fusion cofactor, CXCR4, is rapidly upregulatedwhen T cells are contacted with a solid phase surface comprising anti-CD28 and anti-CD3 antibodies (page 38, lines 19-24). Thus, the Examiner's allegation that treatment of T cells with a solid phase surface comprising anti-CD3 and anti-CD28 antibodies would inherently result in HIV-

1 fusion cofactor ***downregulation*** is unfounded. Those things that will ***always*** flow naturally from that which is disclosed are regarded as being inherent. That which ***may*** occur does not qualify under the doctrine of inherency. That is, probabilities and possibilities are not sufficient to establish inherency.

Furthermore, and importantly, in contrast to the Examiner's allegation, contact of T cells with a solid phase surface comprising an anti-CD3 and an anti-CD28 antibody does not inherently lead to resistance to infection by an M-tropic HIV isolate. This is most clearly articulated by Creson et al. (J. Virol. 73:9337-9347), a courtesy copy of which is provided herewith to assist the Examiner in Appendix B. This reference states that:

> ***Many laboratories*** are currently using the combination of anti-CD3 plus anti-CD28 costimulation ***to recover infectious HIV*** from cells of HIV-positive donors ***with low or undetectable viral loads.*** (page 9343, right column, Discussion).

Thus, costimulation with anti-CD3/CD28, under certain circumstances, can result in ***enhanced replication of M-tropic strains of HIV.*** Yet, in the instant Application, Applicants have surprisingly shown that anti-CD3/anti-CD28 costimulation of T cells generates resistance to infection by M-tropic strains of HIV-1. Furthermore, Creson et al. report that:

> Since continuous plate stimulation caused the down-regulation of CCR5 and increased secretion of β-chemokines, we expected that this method of stimulation also would induce resistance to infection by M-tropic strains of HIV-1. Continuous bead stimulation almost completely inhibited virus replication, and one-time plate stimulation led to high levels of p24 production, as observed in previous experiments. Surprisingly, continuous plate stimulation gave rise to high levels of p24 production relative to those resulting from one-time plate stimulation, in most cases, and sometimes higher. The fact that neither one-time nor continuous plate stimulation consistently leads to lower p24 production suggests that there is no real difference in these two methods of

> stimulation in terms of resistance. ***Thus, continuous plate stimulation does not protect CD4 T cells from HIV replication despite down-regulation of CCR5 and production of β- chemokines.*** These results suggest that down-regulation of CCR5 and production of β-chemokines may not be the only factors that contribute to the induction of resistance by anti-CD28 costimulation. [***emphasis added***]. (page 9343, left column).

Creson et al. conclude that "in our hands, CD4 T cells stimulated by continuous passage on anti-CD3/CD28-coated plates produced high levels of p24 and therefore were not resistant to infection despite down-regulated CCR5 expression and increasing production of β-chemokines" (p.9344, left column, last two lines to right column, first three lines). Thus, in striking contrast to the Examiner's allegation (Office Action, page 4 section 8, paragraphs 7-10), contacting T cells with a solid phase surface does not inherently result in resistance of T cells to infection by M-tropic HIV strains, and this is the case even when CCR5 is downregulated.

Finally, the Examiner has alleged that the use of *in vivo* methodology equivalent to that disclosed in the specification-as filed *for in vitro* experiments suggests that downregulation of HIV-1 fusion cofactors would be an inherent outcome of these methods irrespective of whether the contacting step is *in vivo* or *in vitro* (Office Action, page 4, section 8, paragraph, 7). Applicants respectfully disagree. *In vivo* and *in vitro* methods can have very different outcome as evidenced by Chang:

> it has been suggested that the solid-phase anti-CD3 MAb functions by aggregating the CD3 antigen on the T cell surface. However, when anti-human CD3 is injected ***in vivo the results are the <u>opposite</u> of the in vitro effects***. OKT3 MAb, which is the first MAb ever approved for therapeutic use in vivo, is strongly immunosuppressive and is approved for use as an immunosuppressor for patients receiving kidney transplants. The injection of OKT3 causes rapid depletion of T cells from the circulation. [***emphasis added***]. See column 4, lines 3-13.

Chang teaches that it is not possible to predict whether a method that works *in vitro* would work in a similar manner *in vivo*. This is especially relevant in the instant application because Applicants have taught that a variety of immune factors, including soluble factors and the state of T cell differentiation, as well as indirect factors influence the susceptibility of T cells to HIV-1 infection (page 1, lines 1-38 continuing on page 2, lines 1-10) as evidenced by the observation that lymphocytes from different donors are not equally infectable with HIV-1 (page 1, lines 1-38 continuing on page 2, lines 1-10). Since a variety of immune and indirect factors influence infection by HIV-1 by modulating expression of HIV-1 fusion cofactors, there is no guarantee that a composition would have the same effect *in vivo* as it did *in vitro*. Thus, *in vivo*, expression of HIV-1 fusion cofactors, or the lack thereof, would be dictated by the crosstalk that occurs between multiple different pathways and factors. Taken together, Applicants aver that Chang does not inherently suggest Applicants' claimed invention.

In summary, because Chang does not teach ***each and every limitation*** of Applicants' claims ***either expressly or inherently***, Applicants aver that the ground for this rejection has been overcome. Applicants respectfully request reconsideration of the application in light of the discussion above and withdrawal of this rejection under 35 U.S.C. § 102(e).

VI. Rejection under 35 U.S.C. § 102(e) based on Levine et al.

Claims 1, 55 and 87-90 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Levine et al. (*Int. Immunol.*), as evidenced by Levine et al. (*Science*). Applicants believe that the Examiner has incorrectly applied a rejection under 35 U.S.C. § 102 (e) because the references being cited are not patent applications or issued patents.

Accordingly, Applicants will respond to this rejection as if it were a rejection under 35 U.S.C. § 102(b).

The Examiner alleges that Levine et al. (*Int. Immunol.*) teach a method comprising contacting T cells with a solid phase surface comprising an anti-CD3 antibody and an anti-CD28 antibody *in vitro*.

Levine et al. (*Int. Immunol.*) are directed to investigating differences, if any, between the CD28 ligands, B7-1 and B7-2, in the ability to co-stimulate T cells. Levine et al. do not in any way teach or suggest a method for down-regulating HIV-1 fusion cofactor expression by contacting T cells with a solid phase surface comprising an anti-CD28 antibody and anti-CD3 antibody thereby down-regulating HIV-1 fusion cofactor expression, wherein the T cell is more resistant to infection by an M-tropic HIV isolate than a T cell not contacted with the solid phase surface. Furthermore, as explained in the previous section, resistance to infection by M-tropic viruses and down-regulation of HIV-1 fusion cofactors ***are not inherent properties*** of contacting T cells with a solid phase surface comprising an anti-CD28 antibody and an anti-CD3 antibody. Thus, Levine et al. (*Int. Immunol.*) do not either explicitly or inherently teach each and every limitation of Applicants' claimed invention and thus cannot anticipate it. Applicants respectfully request that this rejection be reconsidered and withdrawn.

VII. Rejection under 35 U.S.C. § 102(e) based on June et al.

Claims 1, 55, and 87-94 stand rejected under 35 U.S.C. § 102(e) as being anticipated by June et al. as evidenced by Levine et al.

The Examiner alleges that June et al. teach a method of activating a population of human T cells to proliferate by contacting the cells *in vitro* with an anti-human CD3

antibody immobilized on a solid phase surface and an anti-human CD28 antibody immobilized on the same surface (Office Action, page 5, section 10).

June et al. are directed to methods for inducing a population of T cells to proliferate by activating the T cells and stimulating an accessory molecule on the surface of the T cells using, among others, a solid phase surface coupled with anti-CD3 and anti-CD28 antibodies. June et al. do not in any way teach or suggest a method for down-regulating HIV-1 fusion cofactor expression by contacting T cells with a solid phase surface comprising an anti-CD28 antibody and anti-CD3 antibody thereby down-regulating HIV-1 fusion cofactor expression, wherein the T cell is more resistant to infection by an M-tropic HIV isolate than a T cell not contacted with the solid phase surface.

As argued for the rejections based on Chang and Levine et al., June et al. also do not inherently disclose Applicants' claimed invention. As discussed in detail above, the unpredictability surrounding whether a T cell would be resistant to infection by M-tropic HIV isolates and whether an HIV-1 fusion cofactor would be upregulated, downregulated or unaffected upon contacting T cells with a solid phase surface comprising an anti-CD3 antibody and an anti-CD28 antibody does not make the resistance to infection by M-tropic HIV isolates and downregulation of HIV-1 fusion cofactors inherent properties of the composition used by Applicants in the claimed invention. Thus, Applicants believe that this rejection has been applied in error and request that it be withdrawn.

Furthermore, Applicants submit herewith, as attached Appendix C, a Declaration under 37 C.F.R. § 1.132 by Dr. Carl H. June that states that the invention

disclosed but not claimed in the reference was derived from the inventor of this application (Dr. June) and is thus not the invention "by another."

Applicants aver that the grounds for this rejection have been overcome. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

VIII. Rejection under 35 U.S.C. § 103 (Chang in view of Shattil)

Claims 1, 55, 60, 75, 91 and 93 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over either Levine et al. or Chang each in view of Shattil.

Levine et al. cannot be used as a prior art reference since it is not by "another" as evidenced by the *In re Katz* Declaration filed November 12, 2002 and the instantly submitted Petition to correct inventorship. Accordingly, Applicants will respond to this rejection as it pertains to Chang in view of Shattil.

The Examiner has alleged that it was obvious to the ordinary artisan at the time of the invention to link antibodies to tissue culture dishes as alternate to beads and also that it was obvious to immobilize antibodies to a solid phase surface via an avidin-biotin complex (office Action, page 7, section 12, fifth paragraph). Applicants respectfully traverse this rejection.

To make a *prima facie* case of obviousness, the Examiner has the burden of showing either that some objective teaching in the prior art or knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Indeed, the prior art must suggest the combination or convey to those of ordinary skill in the art a reasonable expectation of success of making it. *In re Vaeck*, 947 F.2d 488, 20

USPQ2d 1438 (Fed. Cir. 1991). The teachings of the references can be combined only if there is some suggestion or incentive to do so. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 221 USPQ 929, 933 (Fed. Cir. 1984).

As discussed above, Chang has not provided an enabling disclosure for the downregulation of HIV-1 fusion cofactors, by merely providing a wish list of antibodies to T cell surface molecules. It would require undue experimentation for one of ordinary skill in the art to pick and choose antibodies from this list to identify those that result in downregulating HIV-1 fusion cofactors. Also, Chang provides no teaching or suggestion that would allow one of ordinary skill in the art to have any expectation of success to arrive at Applicants' invention. Most importantly, Chang provides no teaching or motivation to one of ordinary skill in the art to use ***any*** of his immunoconjugates to ***downregulate HIV-1 fusion cofactor expression***. Chang could not even have contemplated Applicants' claimed method since CXCR4 and CCR5, were not even known in the art at the time of this disclosure, as HIV-1 fusion cofactors. Furthermore, as stated above, Applicants respectfully assert that downregulating HIV-1 fusion cofactors and modulating T cell resistance to infection by an M-tropic HIV isolate upon contacting T cells with a solid phase surface comprising anti-CD3 and anti-CD28 antibodies, are not inherent properties of this composition. Taken together, Chang does not render obvious Applicants' claimed invention. Since Chang does not render obvious the independent claims 1, 55, 60 and 75, the Examiner's rejection based on the obviousness of the dependent claims, which recite using tissue culture dishes or avidin biotin complexes is rendered moot.

Shattil does not compensate for the deficiencies of Chang. Shattil is directed to a method of identifying compounds that effect integrin activation in intact cells. Nowhere in Shattil is there any teaching or motivation for a method of downregulating

HIV-1 fusion cofactor expression using a solid phase surface having anti-CD3 and anti-CD28 antibodies, wherein the T cell is more resistant to infection by an M-tropic HIV isolate than a T cell not contacted with the solid phase surface.

In summary, Chang in view of Shattil does not render obvious Applicants' claimed invention. Thus, Applicants contend that this rejection has been applied in error and request that it be withdrawn.

IX. Rejection under 35 U.S.C. § 103 (June et al. in view of Chang)

Claims 60, 75 and 87-94 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over June et al. as evidenced by Levine et al. in view of Chang.

The Examiner has alleged that

> one of ordinary skill in the art at the time the invention was made would have found it obvious to apply the method taught by June et al. *in vivo*. Given the teachings of Chang that the same product used by June et al. *in vitro* could also be used *in vivo*, the ordinary artisan would have had a reasonable expectation that the method of June et al. could also be practiced *in vivo*. In view of the teachings of June et al. of the beneficial effect on T cell numbers when T cells are contacted with beads on which anti-CD3 and anti-CD28 have been immobilized, the ordinary artisan would have been motivated to administer the beads *in vivo*; particularly since an *in vivo* method would obviate potential sources of secondary infection due to ex vivo expansion of the T cells and would reduce the risk of exposure of health care workers to HIV infected cells (Office Action, page 8, section 13, last paragraph).

Claims 60 and 75 and claims depending thereon are drawn to methods for downregulating HIV-1 fusion cofactor (or CCR5) by contacting T cells with a solid phase surface comprising an anti-CD3 and an anti-CD28 antibody *in vivo*, thereby downregulating HIV-1 fusion cofactor (or CCR5) expression in the T cell, wherein the T

cell is more resistant to infection by an M-tropic HIV isolate than a T cell not contacted with the solid surface.

As discussed above, in light of the Declaration under 37 C.F.R. § 1.132 by Dr. Carl June, June et al. does not constitute prior art as discussed above.

Furthermore, June et al. do not teach or suggest Applicants' inventive method. As acknowledged by the Examiner (Office Action, page 5, section 10), June et al. teach that T cells can be activated to proliferate *in vitro* with an anti-human CD3 antibody immobilized on a solid phase surface and an anti-human CD28 antibody immobilized on the same surface. However, this reference is silent regarding a method for downregulating HIV-1 fusion cofactors in a T cell by contacting these T cells with a solid phase surface comprising anti-CD28 antibody and anti-CD3 antibody, wherein the T cell is more resistant to infection by M-tropic HIV isolates than a T cell not contacted with the solid surface. The Examiner further acknowledges that June et al "do not explicitly teach the *in vivo* application of the antibody coated solid surface" (Office action, page 8, section 13, paragraph 4). To fill this gap, the Examiner relies on Chang to provide an *in vivo* application for the *in vitro* teachings of June et al. However, Chang explicitly warns :

> it has been suggested that the solid-phase anti-CD3 MAb functions by aggregating the CD3 antigen on the T cell surface. However, when anti-human CD3 is injected ***in vivo the results are the opposite of the in vitro effects***. [emphasis added]. (column 4, lines 3-7).

Because Chang teaches away from extending *in vitro* studies *in vivo*, the Examiner cannot rely on Chang to provide support for extending the *in vitro* teachings of June *in vivo*. As such, June et al. do not render obvious Applicants' claimed invention because activating T cells to proliferate does not in any way read on downregulating HIV-1 fusion cofactors, wherein the T cell is more resistant to infection by an M-tropic HIV

isolate than a T cell not contacted with the solid phase surface. The beneficial effect of increasing T cell numbers in an HIV-patient is entirely different from downregulating HIV-1 fusion cofactors thus making T cells more resistant to M-tropic HIV isolates.

Because June et al. does not constitute prior art for the claimed invention, and because June et al. in view of Chang do not render obvious Applicants' claimed invention, Applicants respectfully request that this rejection be withdrawn.

X. Rejection under the doctrine of obviousness-type double patenting

Claims 1, 55, 60, 75 and 87-94 stand rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,352,694 either alone or in combination with Chang (U.S. Pat. No. 6,129,916).

As discussed above, U.S. Patent No. 6,352,694 does not anticipate instant claims 1, 55 and 87-94 because the instant limitations are neither explicitly nor inherently claimed in U.S. Patent No. 6,352,694. Regarding, instant claims 60 and 75, for the reasons set both above, the application of the method *in vivo* would not be an obvious variation of the method claimed by June et al. in view of the teachings of Chang.

Applicants respectfully contend that this rejection has been applied in error and request its withdrawal.

XI. Conclusion

Applicants aver that all of the outstanding rejections of record have been overcome by amendment and/or argument and/or entry and consideration of the attached Appendices A-C. Accordingly, the claims are now believed to be in condition for allowance. Applicants respectfully request that the Examiner issue a timely Notice of Allowance.

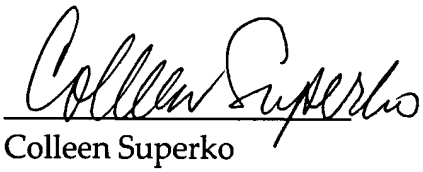
Also, accompanying this Amendment is a Petition for a Three Month Extension of Time for responding to the Office Action. Please charge the fees outlined on the attached Fee Transmittal to our Deposit Account No. 08-0219.

No additional fees are believed to be due in connection with this correspondence other than the fees for the three month Petition for Extension of Time. Please charge any payments due or credit any overpayments to our Deposit Account No. 08-0219.

The Examiner is invited to telephone the undersigned at the telephone number given below in order to expedite the prosecution of the instant application.

Respectfully submitted,

Date: July 17, 2003



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